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## ► To cite this version:

Bram Ruijsink, Konrad Zugaj, Kuberan Pushparajah, Radomir Chabiniok. Model-based indices of early-stage cardiovascular failure and its therapeutic management in Fontan patients. FIMH 2019 - 10th Functional Imaging and Modeling of Heart, Jun 2019, Bordeaux, France. pp.379-387. hal-02186819

**HAL Id: hal-02186819**

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Submitted on 17 Jul 2019

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# Model-based indices of early-stage cardiovascular failure and its therapeutic management in Fontan patients

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**Abstract.** Investigating the causes of failure of Fontan circulation in individual patients remains challenging despite detailed combined invasive cardiac catheterisation and magnetic resonance (XMR) exams at rest and during stress. In this work, we use a biomechanical model of the heart and Fontan circulation with the components of systemic and pulmonary beds to augment the diagnostic assessment of the patients undergoing the XMR stress exam. We apply our model in 3 Fontan patients and one biventricular “control” case. In all subjects, we obtained important biophysical factors of cardiovascular physiology – contractility, contractile reserve and changes in systemic and pulmonary vascular resistance – which contribute to explaining the mechanism of failure in individual patients. Finally, we used the patient-specific model of one Fontan patient to investigate the impact of changes in pulmonary vascular resistance, aiming at in silico testing of pulmonary vasodilation treatments.

**Keywords:** Fontan circulation · heart failure · dobutamine stress · pulmonary vascular resistance · pulmonary vasodilation therapy.

## 1 Introduction

Patients with Fontan circulation – a surgically established circulation for patients with a single functional ventricle in which the systemic and pulmonary circulations are coupled in series – experience a progressive decline in cardiovascular function, ultimately leading to heart failure [6]. Fontan failure (FF) is multifactorial and often involves both the heart and the circulation, e.g. a reduced myocardial contractility, contractile reserve, or an increased pulmonary vascular resistance (PVR). Identifying the exact cause of failure is therefore difficult. A potential treatment option for FF is pulmonary vasodilation (PVD) [4].

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However, its efficacy remains inconclusive, especially in patients without elevated PVR. Several specialised centres use combined cardiac MRI and catheterisation (XMR) at rest and during pharmacological stress to investigate the causes of FF, and to identify patients that might benefit from PVD [9]. These diagnostic exams generate rich datasets of combined ventricular and pulmonary pressures, blood flow and cardiac function. Despite this, understanding the role of each parameter in FF in individual patients remains challenging. We hypothesise that biomechanical modelling may improve the interpretation of XMR exams, and the augmented knowledge of patients’ physiology could be considered in the PVD reactivity testing to possibly reduce its invasiveness.

In this work we build patient-specific models of the Fontan circulation (heart with systemic and pulmonary circulations in series) based on the stress XMR exam, which can provide the values of myocardial contractility, SVR and PVR at rest and their changes during stress. Then, using such an “avatar” of rest and stress physiology from one patient, we investigate the impact of an increased and decreased PVR on the heart and circulation – the changes known to take place with aging and after PVD, respectively.

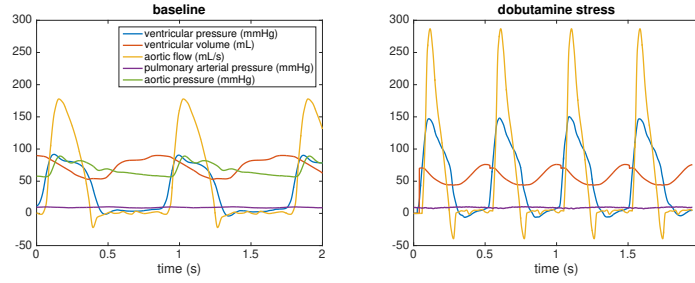
## 2 Methods

### 2.1 Data

Three patients with Fontan circulation (underlying diagnosis: hypoplastic left heart syndrome) and early-stage FF underwent an XMR dobutamine stress exam. During the exam, cine MRI, phase-contrast flow through aorta and branch pulmonary arteries (PAs), together with catheter pressure measurements in the aorta, systemic ventricle and PAs were obtained at rest and during pharmacological stress (infusion of dobutamine  $10 \mu\text{g}/\text{kg}/\text{min}$ ), see Fig. 1. None of the patients had significant collateral flow or fenestration shunts. In addition to the single-ventricular patients, one patient with a biventricular heart was included in the study. This patient suffered from biliary atresia and underwent a stress XMR during work-up for liver transplantation. This study was approved by our regional ethics committee, London UK (Ethics Number 09H0804062) and written informed consent was obtained for all subjects.

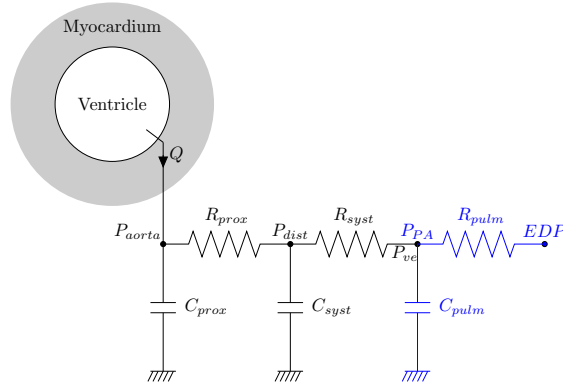
### 2.2 Model

The systemic ventricle is modelled using the multiscale biomechanical model described in [3], of which the geometry and kinematics were reduced to a sphere [2], while all other biophysical properties correspond to the full 3D model. Briefly, the passive part of the myocardium is modelled using the hyperelastic potential by Holzapfel & Ogden [5], and the active component by a system of ordinary differential equations representing chemically controlled actin-myosin interactions generating active stress, of which the asymptotic value  $\sigma_0$  is directly related to myocardial contractility.



**Fig. 1.** Data of a selected Fontan patient acquired at rest and during stress.

The ventricle is connected to the circulation system, represented by a 3-stage Windkessel (WK) model consisting of the very proximal part of the circulation (aorta and large arterial branches with resistance and capacitance  $R_{prox}$  and  $C_{prox}$ ); main part of the systemic circulation ( $R_{syst}$ ,  $C_{syst}$ ); and the pulmonary circulation ( $R_{pulm}$ ,  $C_{pulm}$ ), see Fig. 2. The role of the proximal element is to capture the correct peak aortic pressure. Its effect on the overall ventricular afterload is limited, as  $R_{prox}$  and  $C_{prox}$  are  $\sim 1/10$  of their systemic counterparts. Therefore, we associate systemic vascular resistance (SVR) directly with  $R_{syst}$ , while  $R_{pulm}$  represents PVR.



**Fig. 2.** Scheme of the model of systemic ventricle with the corresponding circulation: 2-stage Windkessel model for biventricular subject (terminating by central venous pressure  $P_{ve}$ ); 3-stage Windkessel with the pulmonary component in blue ( $P_{PA}$  being pulmonary artery pressure, and ending by the end-diastolic ventricular pressure EDP).

In the biventricular case, only a 2-stage WK model was used (without the pulmonary part). For the Fontan patients, in addition to the 3-stage WK, a

circulation with SVR and PVR lumped into “total vascular resistance” (TVR) was calibrated. The role of these 2-stage WK models was to obtain a simpler representation of the afterload against which the systemic ventricle works.

The heart and circulation models were simulated using the MATLAB-based simulator CardiacLab developed at Inria in the team M $\Xi$ DISIM (main contributor Philippe Moireau).

### 2.3 Model calibration

The 3-stage WK model was calibrated sequentially – first the systemic, followed by the pulmonary part. The systemic and pulmonary resistances were initialised using the mean difference of respective pressures (mean aortic, pulmonary artery or terminal end-diastolic ventricular) and cardiac output (CO), as  $R_i \sim \frac{\Delta P_i}{CO}$ . The associated capacitances were pre-calibrated by assuming the time constants (given by multiplication of resistance and capacitance) being 1 second. For a detailed calibration, the measured aortic flow was imposed into the circulatory model firstly with the terminal pressure being the pulmonary artery pressure in the regime of a 2-stage (proximal+systemic) WK to calibrate the systemic part; then, the proximal resistance was adjusted to match the peak aortic pressure; lastly, the ventricular EDP was used as the terminal pressure in the 3-stage WK to calibrate the pulmonary part. For the biventricular “control” case (and to obtain TVR, the lumped SVR and PVR, in Fontan patients), the 2-stage WK was calibrated (i.e. steps 1 and 2 above). The calibration process was performed at rest and during stress.

The heart model was calibrated using the following sequence: First, the geometrical relations in the heart model (ventricular volume and wall thickness) were prescribed using the end-diastolic volume (EDV) and myocardial wall mass obtained from cine MRI. The volume of unloaded ventricle  $V_0$  was assumed to be 50% of EDV [7]. The passive properties of the heart were adjusted by imposing the measured EDP and subsequently multiplying the hyperelastic potential by a “relative stiffness parameter” to obtain the measured EDV. Next, the active properties of the ventricle were adjusted by connecting the calibrated circulation WK model, imposing the timing of the activation (according to the measured ECG), and adjusting the myocardial contractility  $\sigma_0$  to reach the end-systolic volume (ESV) and aortic flow as in the data. After this calibration at rest, the adjustments in the model during stress were obtained by connecting the WK calibrated using the stress data, adjusting the electrical activation according to the observed chronotropic effect, prescribing the preload pressure according to data, and lastly adjusting  $\sigma_0$  to match the observed end-systolic volume (ESV) and aortic flow.

### 2.4 In silico PVD testing

Using the heart-circulation model of a selected Fontan patient, calibrated at rest and stress, we performed an in silico study to investigate the impact of modifying the PVR on pulmonary artery pressure (invasive indicator) and on stroke volume

(SV, non-invasive indicator). The model was run with varying PVR (by factors 0.25, 0.5, 2 and 4), while keeping all other parameters as calibrated for rest / stress). We evaluated the changes in SV and PA pressure in comparison to those in our original calibration.

Patient	contractility rest $\sigma_0^{rest}$ (kPa)	contractility stress ( $\times \sigma_0^{rest}$ )	SVR rest $R_{syst}^{rest}$ ( $\frac{MPa \cdot s}{m^3}$ )	SVR stress ( $\times$ rest)	PVR rest $R_{pulm}^{rest}$ ( $\frac{MPa \cdot s}{m^3}$ )	PVR stress ( $\times$ rest)	TVR rest ( $\frac{MPa \cdot s}{m^3}$ )	TVR stress
FP 1	65	2.4 $\times$	98	1.22 $\times$	11	0.91 $\times$	100	1.25 $\times$
FP 3	73	2.1 $\times$	108	1.62 $\times$	9	1.48 $\times$	125	1.48 $\times$
FP 5	73	2.0 $\times$	171	1.22 $\times$	19	0.76 $\times$	190	1.17 $\times$
CC 1	70	1.4 $\times$	130	0.90 $\times$	N/A	N/A	N/A	N/A

**Table 1.** Summary of the changes in contractility, systemic and pulmonary vascular resistances (SVR, PVR) and total pulmonary resistance (TVR) for Fontan patients (FP) and biventricular control case (CC) during dobutamine stress.

### 3 Results

#### 3.1 Patient-specific heart-circulation models at rest and stress

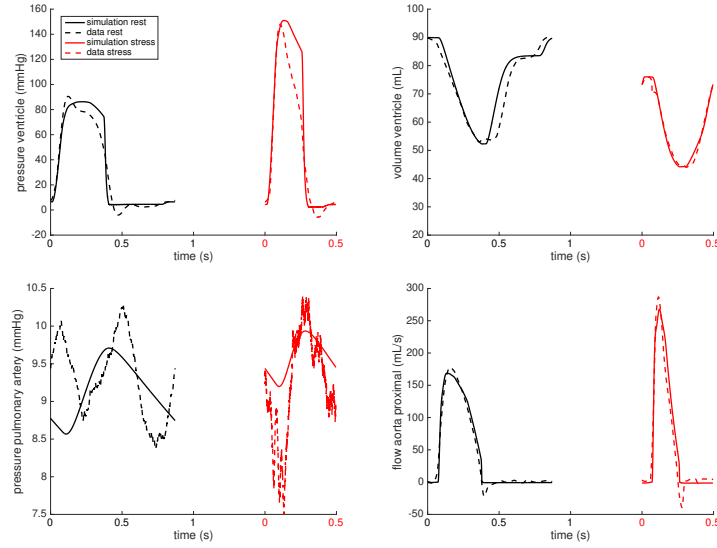
The quantitative values of parameters of the circulation and myocardial contractility are shown in Table 1. Fig. 3 shows the simulated indicators compared with the data for a selected Fontan patient at rest and during stress. Fig. 4 compares the systemic and pulmonary vascular resistances for all patients at rest and their adaptation during stress.

#### 3.2 In silico test of PVD at various physiology stages

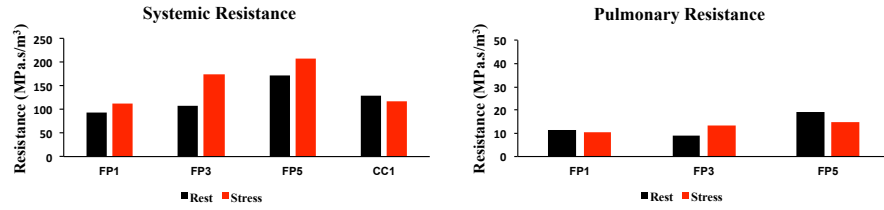
Fig. 5 shows the assumed effect of PVD in Fontan patient 5. The blue marker represents the PVR value obtained from the original calibrations. The mean pulmonary pressures were similar at rest and during stress. SV was higher at rest, compared to stress. With varying PVR, there was a significant change in SV at rest, see Fig. 5. This trend was much less pronounced during stress. Varying PVR did also result in a significant and expected change in average pulmonary pressures, both at rest and during stress.

### 4 Discussion

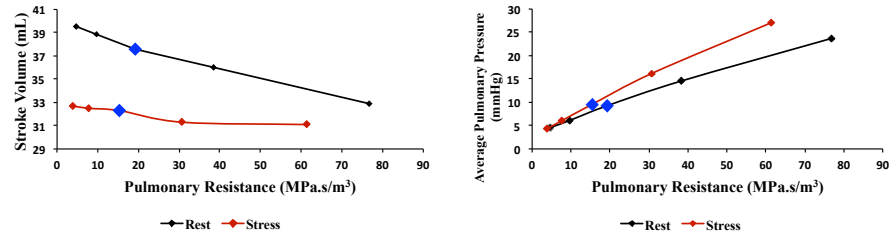
In this study, we explored the use of biomechanical models to investigate factors underlying heart failure in patients with Fontan circulation. We used XMR datasets obtained at rest and during stress to create patient-specific models to



**Fig. 3.** Simulations at rest (black) and during stress (red) for Fontan patient 5.



**Fig. 4.** Systemic and pulmonary vascular resistances at rest (black) and stress (red) in all Fontan patients (FP) and the control biventricular case (CC).



**Fig. 5.** Stroke volume (left) and mean pulmonary pressure (right) response to varying PVR in Fontan patient 5. The blue marker represents the original patient-specific calibrations.

access the biophysical parameters that are not directly available from the data themselves. Good calibrations were obtained for all included cases at rest and during stress: the data-simulation error of maximum ventricular pressure averaged over all subjects and physiological states was 4.7 mmHg; error of mean pulmonary pressure 0.25 mmHg; and error of stroke volume 1.2 mL, see example Fig. 3. This suggests that our proposed model, while simplifying both the heart and circulation, can well describe the different physiological conditions. With such close-to-real-time running models (computation time of one cardiac cycle being  $\sim 10$  seconds on a standard laptop), we were able to obtain fast simulations using standard computers within a clinically relevant time-frame (i.e. compatible with  $\sim 3$ -hour time-frame to clinically evaluate and report the outcomes of the exam).

At rest, myocardial contractility was slightly increased in Fontan patients compared to the biventricular case. However, all Fontan patients had a good contractile reserve ( $> 2\times$  resting values) [1], see Table 1. These results suggest that FF in these particular Fontan patients was not due to systolic dysfunction.

Our coupled model also allowed to investigate the vascular response. At rest, we did not see significant differences in resistance between Fontan patients and the control case. However, during stress the vascular adaptations varied. In the control case, the resistance decreased – an expected response in normal physiology [10]. However, in our Fontan patients the total resistance of the system (TVR) increased. By looking at the changes in resistance of the two in-series-coupled beds (i.e. SVR and PVR), we could see that SVR was the main contributor to the effect, while there was only a relatively small change in PVR. This could reflect a vascular maladaptation of the systemic circulation to the chronic high systemic venous pressures [11] – the result of the circulations coupled in series.

While PVR is only a relatively small component of TVR, clinical and experimental studies have shown that it might have a large impact on cardiac output in the Fontan circulation [11]. This has formed the rationale behind PVD treatment. However, whether all patients benefit from PVD is unclear, especially when PVR is not elevated. We used our calibrated model in Fontan patient 5 to investigate the impact of hypothetical changes in PVR *in silico*, while keeping all other factors of the model as calibrated for rest and at stress (preload, heart rate, contractility and SVR). The model at rest suggests that varying PVR could result in a significant shift in stroke volume – i.e. a non-invasive index – despite the fact that the PVR was not significantly elevated in this patient [8].

The main limitation of our preliminary *in silico* PVD test is that preload was fixed while varying PVR, even though a change in PVR is likely to result in a change in flow towards the heart [8]. We aim to address this limitation by exploiting closed-loop heart-circulation models, once having data obtained during XMR exams that include *in vivo* PVD provocation both at rest and during stress. The approach nevertheless represents an initial step in studying some non-invasive indices, which might contribute to the assessment of PVD in individual patients.



Finally, we aim to further refine the circulatory model to include potential pathological systemic-to-venous or veno-venous shunts, which are often formed in Fontan patients, even though these were not present in our subjects.

## 5 Conclusion

In this paper, we showed that our models allow a detailed investigation of some key biophysical factors of the pathological stress response in Fontan patients. Moreover, we performed first steps in exploring the use of modelling to examine potential changes in PVR on the cardiovascular system. We aim to further investigate modelling in a larger group of patients, loop our models to include venous return and subsequently compare the results of *in silico* PVD experiments to data of prospectively examined patients. Ultimately, we hope to obtain the models that would contribute into the identification of patients who could benefit from PVD, in order to decrease the invasiveness of PVD-reactivity tests.

## Acknowledgments

The authors acknowledge financial support from the Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and the NIHR Cardiovascular MedTech Co-operative (previously existing as the Cardiovascular Healthcare Technology Co-operative 2012–2017), the support of Wellcome/EPSRC Centre for Medical Engineering [WT 203148/Z/16/Z], and from the Inria Associated team ToFMODE. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

In addition, the authors would like to acknowledge Philippe Moireau and Dominique Chapelle, Inria research team MΞDISIM, for providing the cardiac simulation software CardiacLab under a Royalty-free software license.

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